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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,883	01/10/2003	Yoshihiro Urade	2002-0487A	1364

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,883	URADE ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-5 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Urade (1998) Nippon Rinsho Feb;56(2):488-92.

Claims 1-5 drawn to a non-human mammal overexpressing a human hematopoietic prostaglandin D2 (PGD2) synthase gene are anticipated by Urade, who discloses mice overexpressing human PGD2 synthase (see Abstract, lines 4-6), using human cDNA to generate the transgenic mice (see pg. 490 col. 1 parag. 2 lines 5-6). Human hematopoietic PGD2 synthase and human PGD2 synthase are different names for the same synthase. Therefore, Urade clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Urade (1998) Nippon Rishon Feb 56(2): 488-92, and Shichijo et al (1998) Clinical and Experimental Allergy 28: 1228-1236.

Urade teaches a transgenic mouse that overexpresses human PGD2 synthase (see pg. 490 col. 1 parag. 4), for the purpose of studying how overexpression or loss of function of human PGD2 synthase impacts sleep regulation (see pg. 488, Abstract).

Shichijo et al teaches that "little is known about the pharmacological profiles of allergic mediator release from cultured mast cells" (see pg. 1228 lines 2-3). Shichijo et al continues that cultured mast cells release the allergy mediators PGD2, histamine, tumor necrosis factor-alpha, and sulfidoleukotrienes (see pg. 1229 col. 1 parag. 1 lines 8-12), and that "anti-asthma drugs such as mast cell-stabilizing agents, beta-adrenoreceptor agonists, and theophylline are useful for the treatment of asthma, and have been reported to inhibit mediator release from human lung mast cells" (see pg. 1229 col. 1 parag. 2 lines 1-4). Shichijo et al continues to teach that PGD2 release by human mast cells is stimulated by anti-IgE, and is that this release is inhibited by azelastine, disodium cromoglycate (see pg. 1233 col. 2 parag. 2 lines 1-2 bridge pg. 1234 col. 1 parag. 1 lines 1-6), isoproterenol, salbutamol, and clenbutorol (see pg. 1234 col. 1 parag. 2 lines 1-8).

Motivation is provided in the art teaching that mice overexpressing PGD2 synthase were available as taught by Urade. Further motivation is provided by Schichijo et al that PGD2 is a mediator in allergic reactions such as asthma, secreted by human mast cells, and can be inhibited by a variety of drugs.

Thus, it would have been obvious to the ordinary artisan at the time of filing to produce a genetically modified mouse, wherein the modification results in the overexpression of human hematopoietic PGD2 synthase as taught by Urade and that this mouse would be useful for testing

the *in vivo* activity of a candidate anti-allergy medicine in a mouse that overproduces PGD2, given the role of PGD2 in allergic responses as taught by Shichijo et al.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Urade (1998) Nippon Rishon Feb 56(2): 488-92, and Hayaishi (1988) JBC Oct. 263(29): 14593-14596.

Urade teaches a transgenic mouse that overexpresses human PGD2 synthase (see pg. 490 col. 1 parag. 4), for the purpose of studying how overexpression or loss of function of human PGD2 synthase impacts sleep regulation (see pg. 488, Abstract). Urade further teaches that a transgenic mouse overexpressing human PGD2 synthase results in an increased amount of sleep (see pg. 490 col. 2 parag. 1).

Hayaishi teaches that PGD2 exists in the brains of mammals (see pg. 14593 col. 1 parag. 2 lines 12-17), and is produced by prostaglandin synthetase (see pg. 14593 col. 1 parag 2. lines 29-35 bridge to col. 2 parag. 1 lines 1-2). Hayaishi continues to teach that PGD2 when infused into rats at a rate of 0.6 pmol/min, slow-wave sleep was increased by 33% and paradoxical sleep by 56% (see pg. 14593 col. 2 parag. 4 lines 31-33), and that PGD2 induced sleep was indistinguishable from physiological sleep as judged by electroencephalogram and electromyogram (see pg. 14593 col. 2 parag. 4 lines 36-38).

Motivation is provided by Urade teaching that mice overexpressing human PGD2 synthase have an increased duration of sleep. Further motivation is provided by Hayaishi that PGD2 is formed from PGD2 synthetase and when PGD2 is infused into rats the duration of sleep increases.

Thus, it would have been obvious to the ordinary artisan at the time of filing to produce a genetically modified mouse, wherein the modification results in the overexpression of human

hematopoietic prostaglandin D2 synthase as taught by Urade and that this mouse would be useful for testing the *in vivo* activity of candidate sleep controlling substances on a measured sleep condition as taught by Hayaishi.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Urade (1998) Nippon Rishon Feb 56(2): 488-92, and Haberl et al (1998) Mediators of Inflammation 7: 79-84 and Reginato et al (1998) JBC 273 (4):1855-1858.

Urade teaches a transgenic mouse that overexpresses human PGD2 synthase (see pg. 490 col. 1 parag. 4), for the purpose of studying how overexpression or loss of function of human PGD2 synthase impacts sleep regulation (see pg. 488, Abstract).

Haberl et al teach that PGD2 and its metabolites are potent antiproliferative eicosanoids (see pg. 79 col. 1 parag 1. lines 1-2). Haberl et al continue that bone marrow derived mast cells release PGD2 that is rapidly converted to prostaglandin J2 (PGJ2) (see pg. 81 parags. 3-4 and fig. 1-2), and that PGD2 and PGJ2 exert strong antiproliferative activity by inhibiting cell proliferation using *in vitro* models of THP-1 monocytic, HL-60 myeloid leukemic, and murine autonomous mast cell lines (see pg. 83 parag. 2 and figs. 4a, 4b, and 4c). Haberl et al continues to teach that "production of antiproliferative PGD2 metabolites by bone marrow derived mast cells *in vitro* raises the possibility that mast cells exert an anti-proliferative and anti-neoplastic activity by the release of anti-proliferative PGD2 metabolites *in vivo*" (see pg. 84 parag. 5 lines 7-11).

Reginato et al teach that "obesity is due to increased size and number of adipocytes" (see pg. 1855 col. 2 parag. 2 line 1) and that PGJ2, which is a metabolite of PGD2, directly activates

nuclear peroxisome proliferator-activated receptor γ (PPARγ), which increases adipogenesis (see pg. 1855 col. 2 parag. 3 lines 10-12). Reginato continues that PGJ2, through PPARγ ligand stimulates PPARγ activity resulting in stimulation of the adipogenic gene program (see pg. 1858 fig. 4 and text).

Motivation is provided in the art teaching that mice overexpressing human PGD2 synthase were available as taught by Urade. Further motivation is provided by Haberl et al that PGD2 and its metabolites exert an anti-proliferative effect on mast cells, and Reginato that PGJ2 which is derived from PGD2 increases adipogenesis.

Thus, it would have been obvious to the ordinary artisan at the time of filing to produce a genetically modified mouse, wherein the modification results in the overexpression of human hematopoietic PGD2 synthase as taught by Urade and that this mouse would be useful for testing the *in vivo* activity of a candidate differentiation-controlling substance on mast cells and adipose cells in a mouse that overproduces PGD2, given the role of PGD2 in controlling adipocyte and mast cell differentiation as taught by Haberl et al and Shichijo et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C 112, first paragraph, for failing to meet the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a genetically modified non-human animal, wherein the modification results in the overexpression of the human hematopoietic PGD2 synthase gene. However, the specification does not enable the claimed invention because at the time of filing the production of such animals required undue experimentation without a predictable degree of success as explained below.

At the time filing, the skilled artisan would not have regarded the claimed genetically modified animals as having an enabled use. The animals are not disclosed by the specification as having any phenotype associated with a disease or condition associated with overexpression of the human hematopoietic PGD2 synthase gene. The specification describes the mice as having increased invasion of eosinophilic leukocytes in the lung after antigen challenge (see pg. 10 parag. 2 lines 5-7), lowered spontaneous locomoter after lipopolysaccharide administration (see pg. 10 parag. 5 lines 19-24), and increased body weight gain on a high fat diet (see pg. 11 parag. 2 lines 5-9), compared to wild-type mice. Though transgenic human hematopoietic PGD2 synthase mice have significant increases in body weight, allergy response, and sleep the fact that these are increased demonstrates no enabled use.

With regard to the scope of non-human mammals, the specification requires overexpression of the human hematopoietic prostaglandin D2 synthase gene in ES-cells.

However, only mouse ES-cells were known at the time of filing that colonized the germ line. Thus only mouse ES-cells would have been available to make and use the claimed invention. At most the specification enables the production of mice from mouse ES-cells. Only

"putative" ES cells existed for non-mouse species (Moreadith et al., J. Mol. Med., 1997, p. 214, Summary). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith et al. supports this observation as they discuss the historical perspective of mouse ES cells as follows:

"The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the art at the time of filing with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, this is supported by Pera et al. (2000) Journal of Cell Science 113: 5-10 who present the generic criteria for pluripotent ES or EG cells (see pg. 6, col. 2) and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." (see pg. 6, col. 2, last paragraph). Therefore, should an enabled use be found for the claimed mammals and cells, the mammal and cells would be limited to mouse.

Therefore, at the time of filing, the skilled artisan would have had to engage in an undue amount of experimentation without a predictable degree of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3-5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 contains the phrase "expressing a large amount of human prostaglandin D2 synthase" but it is not clear that what a large amount is. It is suggested that the claim be written to state the amount or range of human prostaglandin D2 synthase required.

Claim 4 contains the phrase "sleep-controlling substance" but it is not clear from the specification what type of sleep is being controlled, or if sleep is increased or decreased. It is suggested that the claim be written to state what type of sleep is controlled, or how it is controlled.

Claim 5 contains the phrase " differentiation-controlling" but it not clear from the specification what type of differentiation is being controlled. It is suggested that the claim be written to state what type of differentiation is being controlled.

Claim 5 contains the phrase "obesity condition" but it is not clear from the specification what type obesity condition is being measured. It is suggested that the claim be written to state what type of obesity condition is being measured.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari Ph.D whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 1-571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

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PRIMARY EXAMINER
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